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No. 09-117

IN THE

Supreme Court of the United States

APOTEX, INC. AND APOTEX CORP.,

Petitioners,

v.

SANOFI-SYNTHELABO, SANOFI-SYNTHELABO, INC., AND BRISTOL-MYERS SQUIBB SANOFI PHARMACEUTICALS HOLDING PARTNERSHIP,

Respondents.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF IN OPPOSITION

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Rule 29.6 Statement

The parent corporations and/or the publicly held companies that own 10 percent or more of the stock of Respondents are:

Sanofi-Aventis
Bristol-Myers Squibb Company
Total
L'Oreal

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Statement

This case arises out of Petitioners' ("Apotex's") challenge to the validity of Claim 3 of U.S. Patent No. 4,847,265 (the "'265 Patent"), which claims clopidogrel bisulfate, marketed by Respondents in the United States under the brand name "Plavix®." Plavix® is indicated for the prevention of heart attacks and strokes, and is the most widely-used prescription anticlotting agent.

Following well-established law, both the District Court and the Federal Circuit held that, even if it were assumed that Apotex had made out a case of "prima facie obviousness" based on the structural similarity of clopidogrel, the "dextrorotatory enantiomer," to the previously described "racemic" compound, PCR 4099, three properties that even Apotex's experts conceded were unpredictable amply rebutted that prima facie case. Those three properties were:

- the unexpectedly complete concentration of anticlotting activity in clopidogrel; its opposite, "levorotatory" enantiomer had none;

- the unexpectedly complete concentration of PCR 4099's troubling neurotoxicity (*i.e.*, potential to cause seizures) in the inactive, levorotatory enantiomer; the active enantiomer, clopidogrel, had no neurotoxicity; and

- the unexpectedly favorable crystalline properties of the bisulfate salt of clopidogrel — a salt from which the prior art "taught away" — that made clopidogrel bisulfate unusu-

ally favorable for formulation as an orally administered tablet.

These three properties, in addition to being unexpected, lay at the core of the features of this drug that made it not only novel, but a breakthrough, approvable, safe and marketable drug. Contrary to the expectation of experts for both parties, *all* the activity of the prior art racemate resided in clopidogrel, yet that active enantiomer was devoid of the racemate's convulsive potential. This ensured that the compound was safe enough to win FDA approval. And the unusually favorable constellation of properties of the bisulfate salt (*e.g.*, stability, lack of hygroscopicity, high melting point), made this daily-dosed drug commercially marketable.

In wrongly accusing the court below of a "fixation on unexpectedness or unpredictability" that "clashes with this Court's decisions" (Pet. 14), [1] Apotex notably avoids pertinent aspects of this Court's obviousness jurisprudence, *e.g.*, *United States v. Adams*, 383 U.S. 39, 51-52 (1966) (existence of unexpectedly favorable property supports a finding of non-obviousness). Apotex also equally incorrectly argues that the resolution of this case conflicted with the teaching of *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), about when an invention that results from an approach that is "obvious to try" can be obvious under 35 U.S.C. § 103. (*See* Pet. 12-13.) This case did not even graze that teaching because the in-

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[1] Citations to the Petition are in the form "Pet."; citations to the Petition's appendix are in the form "#a"; citations to the joint appendix submitted in the Federal Circuit are in the form "A#".

ventive approach Sanofi followed was emphatically not "obvious to try," and neither lower court made any such factual finding. Nor could they. This was not a case in which there were "a finite number of identified, predictable solutions" that this Court indicated in *KSR* might support a conclusion that an invention is obvious to try. *See KSR*, 550 U.S. at 421. Moreover, as noted above, the chemical compound claimed here produced results that were not "anticipated," but rather were contrary to the expectations of both sides' experts.

In short, this case is an especially poor vehicle for considering the question Apotex presents or, more generally, the circumstances under which an inventive approach that is "obvious to try" is obvious under § 103.

A. Factual Background[2]

The petition concerns the U.S. patent on clopidogrel bisulfate, marketed in the U.S. by Respondents as Plavix®. Plavix® is an antiplatelet-aggregation drug prescribed to prevent heart attacks and strokes. (A485; A8480-A8481.)

Clopidogrel bisulfate was the successful culmination of a 15-year research program at the French drug company, Sanofi, now known as Sanofi-Aventis. (*See* 4a-12a.) Sanofi began studying a class of compounds called "thienopyridines" in the hope of finding drugs to combat inflammation. (36a.) They

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[2] The facts concerning the invention of clopidogrel bisulfate are also described in the Federal Circuit's opinion. (4a-12a.)

found none that had that property, but serendipitously discovered that some had the ability to inhibit blood clotting. (36a; A12195:25-A12198:2.) Those compounds might therefore be able to prevent heart attacks and strokes.

After considerable work, Sanofi discovered the drug, "ticlopidine," which had potent anticlotting activity. (36a; A12201:2-12.) Unfortunately, after the drug had been marketed for several years in Europe and the United States, it became apparent that ticlopidine, in rare instances, caused serious and potentially fatal, blood disorders. (37a; A12203:25-12205:3.) Sanofi set out to find a safer alternative to ticlopidine. (37a-44a.)

Over the course of several years, Sanofi made and tested over 600 chiral thienopyridines. (61a; A12241:21-A12243:3.) Most failed either because they were not potent enough or were too toxic for clinical use. Sanofi found, however, that a class of thienopyridines that differed from ticlopidine at a certain position in the molecule were potent anticlotting agents and appeared to be better tolerated than ticlopidine. (A12262:13-21; A12263:19-22; A12264:10-A12265:12.) That invention was disclosed and claimed in U.S. Patent No. 4,529,596 (the "'596 Patent"). (*See* 43a-45a.) The '596 Patent disclosed more than a million compounds. (46a; A12395:5-12; A12538:1-3.)

Unlike ticlopidine, the '596 Patent compounds had what chemists called a "chiral center," which meant they could exist in right-handed or left-handed configurations called "enantiomers." (38a; 46a.) All of the compounds the '596 Patent disclosed

were 50:50 mixtures of those two configurations, which are called "racemic." (38a; 46a; A10201:9-16; A12537:8-10.) Unless chemists employ special procedures that either create only one of the two configurations or separate each from the 50:50 mixture, chemical syntheses produce only the racemic form.

Isolating individual enantiomers was then, and still is now, an unpredictable exercise. (100a; A12545:8-17; A12562:23-A12563:19; A28309.) The evidence was that a chemist must choose from a variety of procedures either to create a single enantiomer or isolate one from a racemic mixture (also known as a "racemate"). (100a-101a.) Which, if any, of those procedures, each of which requires multiple choices of reaction conditions and reagents, would work for any specific compound was unpredictable and likely to require considerable trial and error. (61a; A12562:23-A12563:19.)

Of the 600 chiral compounds Sanofi made, Sanofi had only twice attempted (prior to PCR 4099) to obtain the individual enantiomers of any racemic compound. (A10209:21-25; A12215:22-A12217:1; A12241:21-A12243:3.) Both of those racemic compounds (called "PCR 1033" and "PCR 3549") had anticlotting activity but were too toxic to be therapeutically acceptable. (A11211:25-A11212:6; A12222:7-A122234; A12242:25-A12243:3.) In each case, Sanofi was able to separate the individual enantiomers, but separating the enantiomers did not solve the toxicity problem because each enantiomer retained an unacceptable level of toxicity. (37a-43a; A12277:4-19.) In the case of one of those two racemates, PCR 1033, one enantiomer was more active than the other. (A12222:7-A12223:5.) In the case of the other, PCR

3549, the two were equally active. (A12320:23-A12324:11.) Sanofi regarded each of those enantiomeric separations as failures. (A10199:3-6; A12223:18-24; A12321:6-A12324:11.)

In theory, the maximal increase in activity attainable through the separation of enantiomers of a racemic compound would be a two-fold increase in potency: a result that would be achieved only if, as was rare, one enantiomer (after metabolic processing, if any) possessed all the activity and the other possessed none. (Opinion A41; A12920:9-A12924:3; A17875; A19534-19536 (tbls. 1, 2); A19540 (fig. 11); A12215:22-A12217:1.) In practice, the difference in potency between two enantiomers was more often significantly less stark. (57a-58a; A11196:8-A11200:17; A12838:19-A12839:19; A12919:17-A12923:7; A13148:9-11; A19534-19536 (tbls. 1, 2); A19540 (fig. 11).) With respect to the different pharmacological activity of enantiomers, the prior art offered comprehensive tables showing that although enantiomers often differed in their activity, the nearly universal situation was one in which each enantiomer had some activity. (57a-58a.)

Of the compounds described in the '596 Patent, Sanofi chose to develop one, PCR 4099, as a potential anticlotting medicine. (*See* 53a.) PCR 4099 was a racemic compound. Before undertaking that development, Sanofi did not try to obtain the individual enantiomers, but planned to obtain approval and sell it as a racemate. (53a-56a.) Regulatory standards did not require companies to obtain and test the individual enantiomers of racemic compounds as a condition for approval. (*See* 82a.) Indeed, as of 1980, approximately 80 percent of chiral drugs were sold in

racemic form, and that remains common even today. (A11183:6-13; A11205:8-16; A13814; A17873.) Sanofi invested seven years of effort and spent tens of millions of dollars to develop PCR 4099 as a racemic compound. (80a.)

In addition to the difficulty and unpredictability inherent in obtaining individual enantiomers, and Sanofi's own prior failures to improve the toxicity/activity profiles of PCR 1033 and PCR 3549, Sanofi was aware of another disincentive to undertake that exercise. It knew that the thienopyridines were not active as such, but had to be converted ("metabolized") to a different chemical structure in the body before they were effective. But it did not know what that structural change was. (60a; A10214:13-A10215:8; A11209:11-A11210:3.) Therefore, it was possible that obtaining the individual enantiomers (in addition to failing to yield any improvement over the racemate, as had occurred with PCR 1033 and PCR 3549) might be futile if the body's metabolic processes removed the chiral center or caused the enantiomer to revert back into the racemic form.[3] (A11209:12-19.) In fact, the chemical structure of PCR 4099 was such that it would be especially susceptible to "racemization." (*See* A12453:16-A12454:16.)

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[3] Ironically, thalidomide — the example Apotex cited of an inactive enantiomer having the undesirable toxicity — is also an example of that futility. Thalidomide, the nontoxic enantiomer, is converted by the body into the toxic one. Therefore, thalidomide, which has several approved medical uses, is sold in racemic form. (A10235:21-A10237:13; A11204:18-A11205:7.)

Nevertheless, Sanofi decided to try to obtain the individual enantiomers of PCR 4099, to see if that might produce any improvement in the safety profile. (55a-56a.) There was at best a hope, but not an expectation, that might be the result. (79a; A12275:13-25.) While the Sanofi chemists knew that the properties of the two enantiomers might be different, there was no way to predict if they would be different, at least to any meaningful degree. (58a-59a; A10235:14-A10237:23; A13812.)

Sanofi chemist, Alain Badorc, set out to obtain the enantiomers of PCR 4099. (55a-56a; A10209:6-11; A10211:10-16; A12274:25-A12275:12; A13214:4-8.) Initially, he tried techniques that had worked for PCR 3549, but those techniques failed. (65a-66a; A12453:6-15; A12454:10-16; A12459:24-A12461:15; A28281-A28284; A12121:20-24; A12122:12-14; A25895-A25896; A25937-A25938.) As feared, the products "racemized." (*See id.*) Finally, after five months of trial and error, and by using a technique called diastereomeric salt formation, with a combination of solvents, reactants and conditions that were not taught by the prior art, Badorc succeeded in obtaining the two enantiomers of PCR 4099. (67a-69a; A12466:5-A12474:20; A25904; A26699; A26743.)

Those tests gave a striking result: the dextrorotatory enantiomer (clopidogrel) was active, while the levorotatory enantiomer was completely inactive. (75a; A10213:19-A10214:7; A12283:4-11; A13150:3-6; A13151:2-A13153:10; A13254; A13888-A13890; A14919; A14923; A14924; A18412; A8907; A8923.) The enantiomers of PCR 4099 thus exhibited the rare characteristic of "absolute stereoselectivity."

(58a; 75a; A19534-A19536 (tbls. 1, 2); A19540 (fig. 11); A12923:8-A12924:3; A17875.)

When toxicological tests were performed, an even more surprising result was obtained. In a comparative acute toxicity study of PCR 4099 and its enantiomers, convulsions were observed in animals receiving PCR 4099 or the levorotatory enantiomer, but no convulsions were observed in animals receiving clopidogrel. (A12289:11-19; A13001:8-24; A27250-A27251; A27554-A27555.) This was very surprising because, if anything, the prior art had suggested that activity and toxicity might correlate with one another. (23a ("The experts also agreed that activity and toxicity were more likely to be positively correlated, such that a reduction in toxicity would be expected also to reduce the beneficial activity.").) The complete lack of correlation seen here flew in the face of any ordinarily skilled person's expectation.

Based upon the surprising test results for clopidogrel, in April 1987, Sanofi made the decision to abandon further clinical development of PCR 4099. (A10218:15-20; A26000-A26001.) From its synthesis in 1980 up until the decision to discontinue its development, Sanofi had spent tens of millions of dollars developing PCR 4099. The decision to discontinue its development set back Sanofi's effort to market a successor to ticlopidine by four years. (80A; A10220:4-6.)

Another surprise occurred as Sanofi moved forward with the development of clopidogrel. To have a medicine in a form that can be used in practice, it must be solid, stable and not absorb water from the

atmosphere (*i.e.*, it must be "non-hygroscopic"). (74a.) For PCR 4099, which was the mixture of clopidogrel with an equal amount of its opposite enantiomer, the hydrochloride salt met all those requirements. (11a.) However, it was not satisfactory for the isolated clopidogrel enantiomer, because it was hygroscopic and unstable. (A11962:12-18; A12477:12-A12478:11.) Accordingly, to market clopidogrel as a tablet, it would be important to discover a more suitable salt. (69a; A12477:12-A12478:11; A25868.)

Pharmaceutical salt development — the process of combining basic or acidic drugs with acids or bases to form (hopefully) crystalline solids — is a highly unpredictable area of medicinal chemistry. (71a-72a.) Whether a crystalline material will form, and the properties that material will have, are unpredictable. (A11167:19-A11168:23; A11725:20-A11726:1; A11946:12-A11948:1; A12272:13-20; A12569:13-A12571:16; A12746:20-A12747:14.) Scientific articles noted the unpredictable nature of pharmaceutical salt selection. (A17448; A27649; A20708.)

Lacking any guidance from the prior art or its own prior work on thienopyridines, Sanofi searched for a suitable salt through a process of trial and error. Between approximately May and June 1987, more than a year after the successful synthesis of clopidogrel, Badorc and others tested at least 21 different acids in combination with clopidogrel, in search of a salt with the desired properties. (A11974:12-A11975:3; A12397:21-A12398:1; A12477:20-A12480:22; A25868-A25872; A26600; A26603-A26608; A26610-A26615; A26631; A26680; A26681-A26686; A26687-A26692; A26694; A26704;

A26748.) After the results of all the screens were obtained, only the bisulfate salt had the desired combination of properties: high melting point and long-term stability, non-hygroscopicity, and solubility. (A11981:14-18; A12479:7-24; A12773:3-9.)

This result was surprising, and not just because of the inherent unpredictability of salt selection. If anything, the prior art would have taught *away* from using sulfuric acid (the acid used to form the bisulfate salt) to form a salt of clopidogrel. A 1986 article teaches the use of *organic* acids as a substitute for hydrochloric acid when a hydrochloride salt is hygroscopic, rather than strong *mineral* acids, such as sulfuric acid. (*See* A20717-A20720.) Thus, the bisulfate salt would be expected to be more hygroscopic than the hydrochloride. (74a-75a; A12779:12-A12787:10; A27930-A27932; A20717-A20720, (fig. 5), (tbl. 3).) The opposite, however, proved true. Further, the bisulfate anion (unlike other salt anions) had the potential to racemize an enantiomerically pure ester such as clopidogrel, thus recreating the toxicity problems that the separation had eliminated. (74a-75a; A12585:16-20; A12594:18-A12596:5; A28317.) Yet the bisulfate salt of clopidogrel is very stable. (A11981:14-18; A12479:7-24; A12773:3-9.)

In February 1988, Sanofi filed an application for a U.S. patent on clopidogrel and certain of its salts, including the bisulfate (the "'265 Application"). (A15104; A15108.) The examiner of the '265 Application had also served as the examiner of the '596 Patent, and he cited and considered the latter in the examination that resulted in the patent in suit. (85a; A15104; A15107; A15160; A15163; A14909.) On July 11, 1989, the '265 Patent issued.

B. The Proceedings Below

1. The District Court

The action below was commenced by Respondents in 2002 shortly after Apotex filed an abbreviated new drug application ("ANDA") to market clopidogrel bisulfate. (A486.) Apotex admitted infringement of Claim 3 of the '265 Patent, but asserted anticipation, obviousness, obviousness-type double-patenting, and inequitable conduct as defenses. (A322-A326; A486.)

On August 8, 2006, six months after the FDA approved its ANDA, and while suit was pending, Apotex began selling clopidogrel bisulfate. Very promptly thereafter, Respondents moved for a preliminary injunction. On August 31, 2006, the District Court granted Respondents' motion, *Sanofi-Synthelabo v. Apotex, Inc.*, 488 F. Supp. 2d 317 (S.D.N.Y. 2006), and the Federal Circuit affirmed. *Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368 (Fed. Cir. 2006).

A four-week trial occurred during January and February 2007 before Judge Sidney H. Stein. In June 2007, after receiving post-trial briefing from the parties concerning the impact of this Court's intervening, April 30, 2007 decision in *KSR*, the District Court held the patent was not invalid and not unenforceable, and entered a judgment permanently enjoining further infringement. *Sanofi-Synthelabo v. Apotex, Inc.*, 492 F. Supp. 2d 353 (S.D.N.Y. 2007). In a detailed opinion, the District Court found, among other things, that, with respect to the properties of separated enantiomers generally:

> Where there is variation, the extent of that variation is not predictable and can be weak, moderate, or strong — a view confirmed by experts from both parties and credited by this Court . . . . Dr. Robert Snyder, an expert for Apotex, testified that without separating and testing the enantiomers of a particular racemate, a [POSA] could not know what the degree of difference — if any — between the properties of the enantiomers of a racemic compound would be . . . . The prior art, in fact, suggested that 'weak' stereoselectivity — i.e., a difference in activity of 10-fold or less between two stereoisomers — was fairly common and that strong stereoselectivity — i.e., a difference in activity of 100-fold or more between stereoisomers — was less prevalent. . . . Experts from both parties agreed that even today, no scientific principles afford a basis for predicting to what degree, if any, a pair of stereoisomers will exhibit different levels of therapeutic activity and different levels of toxicity.

(58a.)

For that reason, the extreme result that obtained from the separation of the enantiomers here — the complete segregation of activity to only one of the two enantiomers, *i.e.*, "absolute stereoselectivity" — was "uncommon." (58a.) Even more striking and unexpected was that the enantiomer having all the activity, clopidogrel, possessed *none* of the racemate's neurotoxicity; the latter, undesirable property resided solely within the inactive enantiomer. (79a.)

"[A]s experts from both parties agree — it was not possible to predict whether either enantiomer would be . . . more or less toxic — than the other." (61a.)

The District Court further appreciated the complexity of pharmaceutical salt development:

> Formation of a crystalline salt is important for an orally administered drug such as clopidogrel, and the salt form of a drug can affect a drug's pharmacological properties... However, the prior art teaches — and both parties' experts agreed and the Court finds — that whether a crystalline material will form in a particular reaction of acid and base, the type of crystalline material that will form, and the properties that the crystalline material will have, are all unpredictable.

(71a-72a.)

On the basis of these findings, the District Court found further that clopidogrel bisulfate possessed not fewer than three unexpected properties compared to the closest prior art, PCR 4099 and its hydrochloride salt. Specifically, the District Court concluded it was unexpected that (i) all the activity of PCR 4099 would reside in clopidogrel while the levo-rotatory enantiomer would possess none, (ii) the inactive enantiomer would possess all the racemate's neurotoxicity, and clopidogrel none, and (iii) the bisulfate salt would possess a "highly desirable combination of properties," rendering it most suitable for commercial use. (112a-113a.)

In addition to the prior art, which offered no basis for expecting any of the foregoing, the District Court found particularly relevant the actions of Sanofi's own scientists, whom it found to be "skilled":

> Sanofi spent four years and 'tens of millions of dollars' developing and extensively testing the racemate PCR 4099 before deciding to try separating the enantiomers of the racemic mixture . . . . Apotex has not made a persuasive case . . . as to why the skilled chemists at Sanofi . . . would have acted — as Apotex contends — so contrary to the hypothetical [POSA].

(108a.) The District Court also noted that, at conferences, Sanofi representatives made poster presentations and distributed abstracts concerning PCR 4099. It further found that "a person of ordinary skill in the art would not have drawn any inference from those materials concerning the stereoselectivity of platelet inhibition by the enantiomers of PCR 4099" but to the contrary, "would have concluded the PCR 4099 was under development as a promising racemic drug with several positive qualities and no significant reported negative qualities." (55a.)

With respect to Apotex's argument that the decision to separate the enantiomers of PCR 4099 had been influenced by regulatory requirements, the District Court credited the "extensive trial testimony and documentary evidence" showing that Sanofi was not influenced by "any nascent regulatory trend mandating the investigation of enantiomers." (81a-82a.) Applying the factors set forth in *Graham v. John Deere Co. of Kan. City*, 383 U.S. 1 (1966), the

District Court held that Apotex had failed to meet its burden of establishing obviousness by clear and convincing evidence. Although the District Court assumed, "[f]or purposes of analysis . . . that Apotex has made a prima facie case of obviousness" (106a), the District Court concluded that each of the unexpected properties identified above rebutted that prima facie case (107a-111a). Far from ignoring Apotex's "obvious to try" argument, the District Court directly met it, saying: "Whether or not it may have been 'obvious to try' separating the enantiomers of PCR 4099 and, secondarily, preparing its dextrorotatory enantiomer as a bisulfate salt, the wide range of possible outcomes and the relative unlikelihood that the resulting compound would exhibit the maximal increase in antiplatelet aggregation activity and the absence of neurotoxicity makes clopidogrel bisulfate non-obvious." (112a.)

2. The Federal Circuit Appeal

The Federal Circuit affirmed the decision of the district court. *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075 (Fed. Cir. 2008), *reh'g denied*, Mar. 26, 2009. Noting that "the determination of obviousness is dependent on the facts of each case" (citing *Graham*, 383 U.S. 1) (28a), the Federal Circuit upheld the factual findings of the District Court. (30a.) It affirmed the District Court's finding that "a person of ordinary skill would not have had the expectation that separating the enantiomers would be likely to produce an enantiomer having absolute stereoselectivity as to both the favorable antiplatelet activity and the unfavorable neurotoxicity." (30a.) In the latter regard, the court noted the concession of Apotex's expert, who, "when asked whether one could predict

in advance the therapeutic and toxic properties of the enantiomers, stated: 'No. I certainly don't believe you could predict that without separating them and trying it. I can't imagine anybody presuming anything else.'" (23a.)

The Federal Circuit also addressed the *KSR* consideration whether there were "a finite number of predictable solutions" that led to an "anticipated success," *KSR*, 550 U.S. at 421, by affirming the finding "that th[e] separation [of PCR 4099] was not a simple or routine procedure and that success in separation, as well as the allocation of properties, was unpredictable." (25a.) "[N]either the chemists at Sanofi nor a person of ordinary skill in the art could have reasonably expected that the separate enantiomers of PCR 4099 could be obtained at the time that Sanofi was contemplating whether to investigate them and, if obtained, they could not have predicted by what method and configuration." (25a-26a.) And with respect to the unexpectedly favorable properties of the bisulfate salt, the Federal Circuit also affirmed the District Court's findings. "Concerning the bisulfate salt, the district court found no evidentiary support for Apotex's argument that the '596 patent taught the dextrorotatory enantiomer of PCR 4099 as the bisulfate salt . . . . The experts of both parties agreed that whether a pharmaceutically suitable crystalline salt will form from a particular acid-base combination is unpredictable." (26a-27a.)

The Federal Circuit criticized Apotex's arguments for relying on the hindsight knowledge that clopidogrel bisulfate was a useful drug. (26a.) *See Graham*, 383 U.S. at 36 (cautioning against hindsight whereby the teachings of the invention are read

into the prior art); *see also KSR*, 550 U.S. at 421 (recognizing "hindsight bias" and "*ex post* reasoning" as inappropriate in determination of obviousness). "Only with hindsight knowledge that the dextrorotatory enantiomer has highly desirable properties, can Apotex argue that it would have been obvious to select this particular racemate and undertake its arduous separation." (26a.) The Federal Circuit concluded its opinion with a discussion of the consistency of the District Court's reasoning with the patent law principles reiterated in *KSR* (29a-30a), and affirmed the decision of the District Court.

Apotex's petition for rehearing and rehearing *en banc* before the Federal Circuit was denied without dissent.

3. The Pending Reexamination Proceedings

Six months after the Federal Circuit decision rejecting Apotex's challenges, Apotex submitted to the USPTO a request to conduct an *ex parte* reexamination of the '265 Patent. That request relied solely on patents, publications and arguments on which Apotex had unsuccessfully relied in the litigation (and citing as the principal reference the '596 Patent, which was previously cited to and considered by the Examiner in granting the '265 Patent and its Canadian counterpart). On August 17, 2009, the USPTO granted the request, on the ground that there was a substantial new question of patentability, *i.e.*, Apotex submitted to the USPTO some additional prior art that had not been considered in the original prosecu-

tion (but which had been among the exhibits Apotex listed during the trial proceedings below).[4]

Argument

I. The Petition Should Be Denied.

A. The Decisions Below Are Not In Conflict With *KSR*.

As in the proceedings below, Apotex suggests that this Court's decision in *KSR* mandates a finding of Section 103 obviousness for any invention that was "obvious to try," even if the results that were achieved by the invention were not predictable. (Pet. 2, 11.) That position is rejected by *KSR* itself. The relevant portion of *KSR* discussing the circumstances under which approaches that are "obvious to try" may be obvious, expressly contemplates solutions that are "predictable" and that have "anticipated success." 550 U.S. at 421. Indeed, *KSR*'s review of pre- and post-*Graham* decisions reconfirmed that predictability was an essential attribute of any solution that could reasonably be described as "obvious."

For example, *KSR* began its analysis by affirming the principle that "[t]he combination of familiar

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[4] As explained in the Patent Office's Manual of Patent Examining Procedure, Section 2242: "[i]t is not necessary that a 'prima facie' case of unpatentability exist as to the claim for 'a substantial new question of patentability' to be present as to the claim." USPTO filing data published through June 30, 2009 indicate that, since the introduction of the ex parte reexamination procedure in 1981, such ex parte requests have been granted 92% of the time. *See* http://www.uspto.gov/web/ patents/documents/ex_parte.pdf (accessed September 24, 2009).

elements according to known methods is likely to be obvious when it does no more than yield *predictable* results." 550 U.S. at 416 (emphasis added). It then compared the outcome in *Adams* (where the invention was found nonobvious) to the outcome in *KSR* because "[t]he fact that the elements [in *Adams*] worked together in an *unexpected* and fruitful manner supported the conclusion that Adams's design was not obvious to those skilled in the art." 550 U.S. at 416 (emphasis added).

By contrast, the inventions in *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57 (1969), and *Sakraida v. Ag Pro, Inc.*, 425 U.S. 273 (1976) (which *KSR* also discussed, 550 U.S. at 416-17), were found obvious because the component parts functioned just as they were expected to function, *Anderson's-Black Rock*, 396 U.S. at 60-62, and the combination of elements "yields no more than one would expect from such an arrangement," *Sakraida*, 425 U.S. at 282. As *KSR* summarized: "If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability." *KSR*, 550 U.S. at 417.

Contrary to Apotex's assertions, the two courts below gave appropriate weight to *KSR* and its rationale. The Federal Circuit directly addressed *KSR* by name and concluded that the District Court's fact findings and conclusions were fully consistent with it. (29a-30a.) And although the District Court did not mention *KSR* by name, it received post-trial briefs directed specifically to that case, and assumed *arguendo* that Apotex had made out a *prima facie* case of obviousness (which is the only benefit Apotex

could have obtained from a finding that clopidogrel was "obvious to try"):

> Whether or not it may have been "obvious to try" separating the enantiomers of PCR 4099 and, secondarily, preparing its dextrorotatory enantiomer as a bisulfate salt, the wide range of possible outcomes and the relative unlikelihood that the resulting compound would exhibit the maximal increase in antiplatelet aggregation activity and the absence of neurotoxicity makes clopidogrel bisulfate non-obvious.

(112a.) In fact, because routes to obtaining individual enantiomers required multiple choices, much trial and error, and no assurance of success, the case here does not even reach *KSR*'s threshold of "a finite number of identified, predictable solutions." 550 U.S. at 421. Nor was the outcome an "anticipated success." *Id.* As Apotex's expert, when asked whether one could predict in advance the therapeutic and toxic properties of the enantiomers, stated: "No. I certainly don't believe you could predict that without separating them and trying it. I can't imagine anyone presuming anything else." (23a.)

For those and other reasons, it was hardly "obvious to try" to separate the enantiomers of the racemate to obtain a significantly more potent compound. Because the prior art showed that the activities of enantiomers generally differed to only a moderate degree, the far more promising chemical development strategy was to transform racemic compounds into other, distinct racemic compounds, a strategy that would often generate far more striking,

several-fold differences in activity. (A12215:22-A12217:1.) And if the goal was, as here, to eliminate the racemate's toxicity, nothing in the prior art suggested that enantiomeric separation would accomplish that; indeed, Sanofi's own experience with two prior racemic thienopyridines suggested it would not. (61a; A10214:13-A10215:8; A10199:3-6; A12223:18-24; A12321:6-A12324:11; A12638:17-A12640:9.) Further militating against enantiomeric separation was the circumstance that separating enantiomers often — as here — involved difficult chemistry, in which the prior art offered little guidance, and there was no assurance that any of the many techniques organic chemists could use would work. (A11739:22-A11740:6; A11743:15-A11744:4; A24459.) This was, accordingly, not a case in which "the prior art discloses the method of making an article having the characteristics of the patented product." *Gen. Elec. Co. v. Jewel Incandescent Lamp Co.*, 326 U.S. 242, 248 (1945). And even if a technique did work, the possibility that metabolic processes would convert enantiomerically separated compounds back into racemates (as happens with thalidomide (A10235:21-A10237:12; A11204:18-A11205:7)), made the possibility of achieving elimination of toxicity through enantiomeric separation slimmer still. (A10235:14-A10237:13; A12277:4-A12281:21.) For this reason, the Federal Circuit correctly observed that "this case does not concern a combination of familiar elements as in the *KSR* mechanical device." (30a.) It was far more like the throwing of "metaphorical darts at a board filled with combinatorial prior art possibilities," in which the Federal Circuit has held that it remains improper to equate "obvious to try" with

Section 103 obviousness. *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009).

Underscoring the nonobviousness of the decision to try to separate enantiomers, was that Sanofi, an experienced, established pharmaceutical company, rarely did it. The evidence showed that during the clopidogrel development process, Sanofi synthesized 600 racemic compounds, but tried to separate the enantiomers of only three. (61a.) And Sanofi dedicated years and millions of dollars to the development of clopidogrel's racemate, only later to try to isolate the enantiomers. (80a-81a.) That investment and approach would not have made sense if it had been in fact "obvious to try" to separate enantiomers from the outset.

The mischaracterization of this case as one in which there were a "finite number of identified, predictable solutions" is also underscored by the findings that the properties of bisulfate salt were not predictable. The eventual discovery that, among all of the possibilities, only the bisulfate salt had the requisite stability and lack of hygroscopicity was taught away from by the knowledge in the art. According to the prior art, hygroscopicity, the chief defect in the hydrochloride salt of clopidogrel, could be remedied by using an *organic* acid to form the salt (not an inorganic acid, like sulfuric acid, which forms the bisulfate). (74a-75a; A12779:12-A12787:10; A27930-A27932; A20717-A20720, (fig. 5), (tbl. 3).) And sulfuric acid, a strong, inorganic acid, posed the risk of racemizing the clopidogrel enantiomer, thus re-generating the risk of neurotoxicity problems that separation had unexpectedly solved. (74a.) It was not obvious that trying any acid offered "anticipated

success," *KSR*, 550 U.S. at 421, of yielding a favorable salt.

This was not a case like *Pfizer v. Apotex*, where the problem to be solved, the elimination of the potential for "Michael addition" reactions that produced impurities, could be solved by using one of only a few acids whose chemical structure rendered it predictably (according to standard organic chemistry textbooks) invulnerable to that type of reaction. 480 F.3d 1348, 1362 (Fed. Cir. 2007). *See also Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1359-60 (Fed. Cir. 2007) (discussing *Pfizer*; "other publications [ ] disclosed the chemical characteristics of the besylate salt."). The problem here was to obtain a crystalline salt with favorable properties, a problem on which the prior art provided — and still provides — no guidance other than the trial and error approach Sanofi followed. *Cf.* 35 U.S.C. § 103(a) ("Patentability shall not be negatived by the manner in which the invention was made.").

Mindful that this was a case in which there was an abundance of unpredictable outcomes, Apotex sets up the strawman that the Federal Circuit finds an invention nonobvious if there is *any* degree of unpredictability. To that end, Apotex unfairly characterizes the governing standard as inquiring whether there are "at least some unpredictable properties" or whether "certain aspects of the art are inherently unpredictable" or "not-fully-predictable." (Pet. 11, 12, 17.) But the Federal Circuit and its predecessor court have consistently held that, while unexpected and unpredictable results are relevant to the determination of obviousness, they are not automatically conclusive. *See, e.g., Sud-Chemie, Inc. v. Multisorb*

Techs., Inc., 554 F.3d 1001, 1009 (Fed. Cir. 2009) ("[E]vidence of unexpected results . . . will not necessarily overcome a strong prima facie showing of obviousness."). Rather, they are to be evaluated both for their significance and their weight. *See Pfizer*, 480 F.3d at 1369-72; *In re May*, 574 F.2d 1082, 1095 (C.C.P.A. 1978) ("[A]ppellants here have established a substantial record of unpredictability vis-à-vis a highly significant combination of properties."); *In re Nolan*, 553 F.2d 1261, 1267 (C.C.P.A. 1977) (properties of higher luminous efficiency and lower peak discharge current, though unexpected, did not rebut prima facie case of obviousness).

In re May is especially on point. As here, it involved the patentability of an enantiomer when its racemate was known in the art. As here, the unexpected properties were the separation of the desired activity (analgesia) from the undesirable adverse effect (physical dependence). *May*, 574 F.2d at 1084, 1086. The court explained:

> Since the record reflects both an expected beneficial result, viz., potent analgesia, and an unexpected beneficial result, viz., non-addictive, potent analgesia, it is necessary to determine the weight to be accorded each prior to making the ultimate determination on the issue of obviousness.

Id. at 1092. Accordingly, the court found the balance supported a finding of nonobviousness because of both the degree of unpredictability and the significance of the unexpected results. *Id.* at 1093.

Apotex unfairly characterizes the Federal Circuit's decision here when it asserts: "In hanging patentability on this 'known unknown,' the Federal Circuit essentially said that any element of unpredictability or unexpectedness in an experiment suffices to patent the result." (Pet. 14.) Instead, and consonantly with *May* and other cases, the Federal Circuit found that the properties of clopidogrel bisulfate were both unexpected and significant: "[A] person of ordinary skill would not have had the expectation that separating the enantiomers would be likely to produce an isomer having absolute stereoselectivity as to both the favorable antiplatelet activity and the unfavorable neurotoxicity." (30a.)

B. Enantiomer Patents Do Not Require a Special Obviousness Standard.

Apotex also argues that this case is especially certworthy because it involves the patentability of an enantiomer over a previously known racemate. (Pet. 24.) While, to be sure, the Federal Circuit has assessed the validity of a number of patents on separated enantiomers, the analytical approach it has followed is not unique to this corner of pharmaceutical science. Rather, it has been consistent with the approach followed for any other chemical invention, indeed, for any invention of any nature. The Court looks to whether it was routine or difficult to obtain the claimed enantiomer, and whether the properties of the isolated enantiomer were predictable or unexpected.

Thus, patentability has been sustained in cases where, as here, the facts showed that obtaining the enantiomer involved considerable difficulty and/or

the enantiomer, when obtained, displayed properties that were significant and unexpected versus its racemate. *Forest Labs., Inc. v. Ivax Pharms., Inc.*, 501 F.3d 1263, 1269 (Fed. Cir. 2007); *May*, 574 F.2d at 1092-93. Conversely, when the enantiomer was obtained by following established chemistry and its properties were predictable from prior experience with closely-related compounds, the Federal Circuit has not hesitated to find the resulting claim obvious. *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1302 (Fed. Cir. 2007) (the patented stereoisomer's potency was "precisely what one would expect, as compared to a mixture containing other, inert or near-inert stereoisomers."); *In re Adamson*, 275 F.2d 952, 955 (C.C.P.A. 1960). There is, therefore, no intracircuit conflict in the legal analysis applied by the panels in those areas; merely a difference in the factual predicates on which the decisions turned.

C. *KSR* Did Not Reject the Principle that "Obvious to Try" Is Generally Not the Standard for Obviousness Under 35 U.S.C. § 103.

Even if any court had made a finding that the approach here had been obvious to try — and none did — that would not make this case appropriate for this Court's review. On the circumstances under which a solution that is "obvious to try" may be obvious under 35 U.S.C. § 103, the Federal Circuit has faithfully and correctly applied this Court's teaching in *KSR*, and, here too, as in the specific context of enantiomer patent cases, there is no intracircuit split requiring this Court's attention. Apotex's cynical assertion that case outcomes "depend in large part on

who the panelists are" (Pet. 20) and its rhetorical, unsubstantiated allusion to "entrenched confusion" in the Circuit (*id.* at 11) do not withstand a methodical review of the post-*KSR* caselaw.

Heeding *KSR*, the Federal Circuit has struck down some patent claims when the solution they cover would have been obvious to try, in the sense that it combined known elements having known, predictable outcomes/properties. That was the case in *Kubin*, where the claim covered isolation of a polynucleotide coding a specific protein using known biotechnological techniques. *Kubin*, 561 F.3d at 1361. It was also true in *Muniauction, Inc v. Thomson Corp.*, 532 F.3d 1318, 1326-27 (Fed. Cir. 2008), where the claim covered a system for holding internet auctions of municipal bonds and where the prior art disclosed systems for holding internet auctions of other goods. And last month, the Federal Circuit upheld a finding that a claim to the formulation of a known contraceptive drug as a non-enterically coated pill was unpatentable because it would have been obvious to try to formulate the drug as such an ordinary pill, notwithstanding the potential for the drug in the pill, if not enterically coated, to degrade ("isomerize") in the stomach. *Bayer Schering Pharma AG v. Barr Labs., Inc.*, 575 F.3d 1341, 1350 (Fed. Cir. 2009).

But, in keeping with the general principle, unaltered by *KSR*, that "obvious to try" does not mandate a finding of Section 103 obviousness in areas where the possibilities are numerous not "small" or "easily traversed," *Ortho-McNeil Pharm., Inc. v. Mylan Labs, Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008) — and the results not predictable, *In re O'Farrell*, 853

F.2d 894, 903 (Fed. Cir. 1988), the Federal Circuit (as Apotex acknowledges (Pet. 19-20)) has upheld claims against challenges that their inventions were merely "obvious to try." *See Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1351 (Fed. Cir. 2008) ("[O]bviousness of selection of components, when there is no prediction in the prior art as to the results obtainable from a selected component, differs from the issue in KSR . . . ."); *Takeda*, 492 F.3d at 1364 (Fed. Cir. 2007) (upholding claim on diabetes drug). It is no accident that these latter, post-*KSR* cases have been drug patent cases. The interaction of chemical compounds with living cells is among the more unpredictable areas of science. *See, e.g., Mycogen Plant Science v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001) (characterizing chemistry and biology as "unpredictable arts"). *See generally Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353 (Fed. Cir. 2008) ("To the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on these 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable.").

D. The Petition Raises No Serious Public Policy Issue.

Finally, and despite Apotex's rhetoric, this is not a petition that raises a serious public policy issue. The '265 Patent is not a patent of the "evergreening" or "lifecycle extension" variety, *cf., e.g., Bayer*, 575 F.3d at 1343-45, one that extends the intellectual property protection of a compound that is already patented, developed, and on the market. Rather, the '265 Patent was a patent on a new, breakthrough drug compound that took years and millions of dol-

lars to develop. Although the predecessor compound, the racemate, entered development and was itself the object of years and millions of dollars in development costs, it never reached the market; Sanofi discontinued its development in 1987 — *before* applying for the patent-in-suit — because of its troubling neurotoxicity. (80a-81a.) The invention that the '265 Patent claims, exemplifies the highly technical, resource-intensive innovation the patent laws and the Hatch-Waxman Act were intended to encourage; innovation that resulted in the development of the world's second most widely prescribed drug (after Lipitor), and which has saved thousands, if not millions of lives. As noted, the life/pharmaceutical sciences are the antithesis of the mechanical arts; unpredictability here is the rule, not the exception. It is alarmist hyperbole when Apotex predicts that, under the Federal Circuit's decision, "[i]f any degree of unpredictability or unexpectedness sufficed to impart patentability, then virtually every new substance could be removed from the public domain for at least 20 years," because "it will never be possible to predict all of the properties of a new substance." (Pet. 23-24.) As explained above, the Federal Circuit has made plain that, for unexpected results to tip the balance in favor of nonobviousness, they must be significant and evaluated in the context of the entirety of the invention: its expected as well as its unexpected properties. If the substance is truly new — as clopidogrel bisulfate was — and if it produces results that are both unexpected and significant, as clopidogrel bisulfate does, it is entirely consistent with the goals of the patent system to grant to the scientists who create it a statutory right to exclude for a limited term.

Conclusion

For the foregoing reasons, the Petition should be denied.

Respectfully submitted,

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